REMARKS

The Amendments

Claim 9 is clarified to address the new 35 U.S.C. §112, second paragraph, rejection. The amendment does not narrow the scope of the claims.

Applicants reserve the right to file one or more continuing and/or divisional applications directed to any subject matter disclosed in the application which has been canceled by any of the above amendments.

The Rejection under 35 U.S.C. §112, first paragraph

The rejection of claims 1-10, 12 and 23-32 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement is respectfully traversed.

Applicants maintain their position that the claimed compounds and methods of use are adequately enabled by the original disclosure when taken in view of the knowledge of one of ordinary skill in the art. Applicants maintain that, despite the disclosures in the Nicolau (U.S. Patent No. 6,441,186) cited to support the rejection, the PTO has not sufficiently met its burden of refuting the inventors' statements in the application regarding how to make and use the invention. The burden lies first with the PTO to provide evidence or objective reasoning substantiating the allegation that the enabling disclosure is not commensurate in scope with the claims; see, e.g., In re Marzocchi et al., previously cited. In accordance with Marzocchi, the terms of the instant claims correspond in scope with the disclosure regarding the use of the compounds in "treating a disease associated with proliferative processes" (i.e., claim 24) and specific embodiments of such diseases (i.e., claim 25). See, e.g., the disclosure at page 6, last full paragraph, of the instant specification. Also, the terms of the instant claims correspond in scope with the disclosure regarding the use of the compounds in "treating a primary tumor and/or metastases that are not operatively accessible" (i.e., claims 26-28). See, e.g., the disclosure at the paragraph bridging pages 6-7 of the instant specification. The current Office Action cites Nicolau (as discussed further below) but still fails to provide an explanation of *why* it doubts the truth or accuracy of these and other statements of the inventors supporting the use of the claimed compounds. The reliance on Nicolau fails to provide a sufficient basis for any such assertion. The objective evidence of record and known to one of

ordinary skill in the art, including Nicolau but considered with the other evidence already of record (e.g., U.S. Patent Nos. 6,982,276 and 7,008,936) is, in fact, contrary to shedding doubt on the inventors' statements. See, e.g., the paragraph at the top of page 2 of the disclosure pointing out the knowledge in the art of the very high anti-proliferative activity of epothilone compounds, i.e., the class to which the structure of the effector part of the conjugate of formula (I) belongs. Such anti-proliferative activity of the epothilone class of compounds was well known to those of ordinary skill in the art; see, e.g., U.S. Patent Nos. 6,982,276 and 7,008,936, as just a sample of other references in the art.

The evidence in Nicolau alleged to contradict that applicants epothilone conjugate compounds would be useful in treating diseases associated with proliferative processes and particularly for treating a primary tumor and/or metastases is not convincing on this point, particularly in view of the other evidence contradicting it. The general teaching of Nicolau considered as a whole is that epothilones and analogs thereof are expected to have high clinical value due to their toxicity against tumor cells. For example, Nicolau states (col. 1, lines 29-31): "Epothilones are reported to be about 2000-5000 times more potent than Taxol with respect to the stabilization of microtubules." Nicolau also states (Abstract) that: "Several of the analogs are demonstrated to have superior cytotoxic activities as compared to epothilone A or epothilone B." Further, Figures 22 and 23 show that all the epothilone analogs tested by Nicolau demonstrated activity in stabilizing microtubules and in inhibiting human cancer cell lines.

The Office Action points to the remote statement within Example 5 that "the 4,4-ethano-epothilones proved inactive." However, such statement is not supported by any actual data nor is it provided in any context to determine what was intended by "inactive." It also doe not indicate to which 4,4-ethano-epothiolones they are referring. Generally, activity profiles of related compounds provide a sliding scale of activity and the probability that a compound related to a compound which is highly active would exhibit absolutely no activity is low. Instead, in the absence of any actual data in Nicolau, one of ordinary skill in the art would have interpreted this statement as meaning that certain 4,4-ethano-epothilones did not meet the threshold assigned for assessing activity in that particular assay. One of ordinary skill in the art would have no basis to conclude from this isolated statement that the 4,4-ethano-epothilones would have no anti-tumor activity whatsoever. This is

particularly the case when the other evidence of record -- including the new evidence discussed below -- is considered, since Nicolau provides no actual data to support the statement.

Additionally, applicants submit further evidence herewith supporting the activity of the epothilone compounds. Attached is a Declaration under 37 C.F.R. §1.132 submitted in another application (US Ser. No. 09/485,292) directed to epothilone derivative compounds and use thereof. While the declaration was submitted in that application for the purpose of showing the advantage of 10-ethyl or higher alkyl epothilone derivatives over the corresponding 10-methyl epothilones, the data demonstrate that all the epothilone analogs tested exhibited significant levels of activity in a number of assays connected with anti-proliferative activity. All of these compounds contain, at the position corresponding to the 4,4-position according to Nicolau's nomenclature, dimethyl substitution or spirocyclobutyl substitution. This is significant because the 4,4-ethano-epothilones alleged in Nicolau to be "inactive" fall intermediary between these two structures, i.e., the 4,4-ethano group is a spirocyclpropyl group which has the same number of carbons as the dimethyl analog but has the steric hindrance like the spirocyclobutyl analog and is the adjacent homolog thereto. In view of this evidence and the absence of any actual data in Nicolau, one of one of ordinary skill in the art would find it highly unlikely that Nicolau actually found or meant to imply complete absence of activity for the 4,4-ethano-epothilones. In view of this data in assessing the evidence as a whole, it is again urged that the PTO's burden of proof is not met.

Even if Nicolau's statement were correct that some 4,4-ethano-epothilones are totally inactive, such would not support non-enablement for applicants' claims as a whole. First, Nicolau does not identify which 4, 4-ethano analogs it is referring to and certainly they did not test all of them. Further, the law is clear that the inclusion of a relatively small number of inoperative species within the generic scope of the claim does not render the claim invalid for non-enablement. See, e.g., Atlas Powder Co. v E.I. DuPont De Nemours & Co., 224 USPQ 409, 414 (Fed. Cir. 1984), stating:

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude .. possible inoperative substances.'

As held therein, only if the number of inoperative embodiments is significant does the

possibility of invalidity arise. Nicolau does not indicate which specific 4,4-ethano analogs would allegedly be inoperative so no support is provided that a large number of them would be inoperative. In any event, this would only be a small portion of the scope of applicants' claims.

For all of the above reasons, it is urged that the PTO has not met its initial burden of proof of non-enablement and, at least for this reason, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Office Action also refers to four of the "Wands" factors in the enablement rejection. Actually, the Wands decision pointed to consideration of eight factors, thus, it can only be assumed to be admitted that the other four factors not addressed in the office action weigh in favor of enablement. It is further noted that these factors are all considered together and, thus, one will not alone support lack of enablement. Applicants urge that a balancing of all of these factors does not support a non-enablement rejection. Applicants have the following comments regarding each factor:

- Breadth of Claims - The scope of the methods treated is no broader than the acknowledged and known activity in the art of epothilones as anti-proliferatives. Applicants' invention recognizes the previous art of epothilone analogs as anti-proliferatives and does not rely on this aspect for novelty. Thus, the breadth of the claims as to encompassing epothilone analogs is not a proper basis upon which to allege non-enablement. The activity and use of epothilone analogs relied on for the invention is known to those of ordinary skill in the art. Instead, the invention is characterized, in part, by the conjugation of the epothilone with a linker-recognition unit. In this respect, the claim is not particularly broad since it specifies the positions of the linking L groups and the structure of the linkages and also the structure of the EG recognition units attached by the linking groups.
- State of the Prior Art - As admitted in the Office Action, epothilones are known as antiproliferatives and anti-tumor agents. This factor weighs heavily in support of enablement since it would not involve undue experimentation for one of ordinary skill in the art to use applicants' novel conjugate compounds in methods analogous to the known methods. There is no allegation in the Office action that the state of the prior art supports non-enablement.

- Nature of the Invention - As pointed out above, the nature of the invention lies, in part, on the conjugation of the epothilone with a linker-recognition unit and there is no allegation in the Office action that the nature of the invention supports non-enablement.
- Level of Ordinary Skill - The M.D. or Ph.D. skill level, admitted in previous Office actions, is a very high skill level which also weighs in favor of a finding of enablement. There is no allegation in the Office action that the level of ordinary skill supports non-enablement.
- Predictability in the Art - Applicants submit that the level of unpredictability is not particularly high given the admitted state of the prior art regarding epothilone analogs and the ability of one at a high level of skill in the art to analogously apply applicants conjugate compounds to the known uses of epothilones. The allegations of unpredictability based on the Nicolau reference are discussed above and that discussion is incorporated herein by reference. Further, the standard for enablement is not absolute predictability but only reasonable expectation of success; see In re Wright, 999 F.2d 1557, 27 USPQ2d 1510,1512 (Fed.Cir. 1993).
- Direction Provided by Inventor - As discussed above, the specification points out the known activity of epothilones and the specification exemplifies a number of particular diseases for which an antiproliferative effect is desired. The knowledge of one of ordinary skill in the art as to the antiproliferative effect of epothilone analogs is also applicable here. Further, there is no allegation in the Office action that this factor supports non-enablement.
- Existence of Working Examples - Although there are no working examples of methods of treatment in the disclosure, the law is clear that it is not necessary to provide working examples in order to enable the invention; see, e.g., In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970); and, In re Angstadt, 537 F.2d 498, 190 USPQ 214 (CCPA 1976). The known antiproliferative effect of epothilone analogs makes confirmation of such known fact in this application unnecessary. Although unnecessary, the data provided in 132 Declaration filed herewith, support the activity of a epothilone analogs in assays which support their antiproliferative effect.

- Quantity of Experimentation Needed - Applicants respectfully submit that the quantity of experimentation needed is not excessive because the type of experimentation that one of ordinary skill in the art would need to conduct is only routine experimentation due to the known activity and uses of the epothilone analogs and the high level of skill in the art. That some experimentation is required does not support a finding of non-enablement; lack of enablement only arises when the experimentation required is undue. The Office Action states that there is no way to predict which compounds will be active. It may be true that it cannot be absolutely predicted a priori whether a particular compound will be active, but absolute predictability is not required. As pointed out above, based on the knowledge in the art (and supporting data in the art and in the 132 Declaration) one of ordinary skill (a high level of skill here) in the art could reasonably expect that the epothilone analogs will exhibit an antiproliferative effect and would only need to conduct routine experimentation to determine such.

In applicants' opinion, the above factors clearly balance in favor of the instant claims being enabled to one of ordinary skill in the art. There is no basis to suggest that one of ordinary skill in the art could not use applicants epothilone conjugate compounds in methods substantially analogously to methods in which known epothilone analog compounds are used.

For all of the above reasons, it is urged that the specification viewed in light of the knowledge of one of ordinary skill in the art (a high level of skill here) adequately teaches how to make and use the claimed invention. Thus, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

The Rejection under 35 U.S.C. §112, second paragraph

It is believed that the amendment to claim 9 renders the rejection of that claim under 35 U.S.C. §112, second paragraph, moot. The claim now refers to the portion of the compound which does not include the linker-recognition unit of formula (III). Further, the last two lines of the claim clarify that "the hydrogen atoms are replaced by radicals L^1-L^3 in the positions indicated in formula (I)." Thus, this claim defines a preferred embodiment for the structure of the epothilone part of the conjugate compound and clearly states that the radicals L^1-L^3 are then provided thereon. It is

believed that the meaning of the claim, as amended, would be clear to one of ordinary skill in the art.

It is submitted that the claims are in condition for allowance. However, the Examiner is kindly invited to contact the undersigned to discuss any unresolved matters.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,

/John A. Sopp/
John A. Sopp, Reg. No. 33,103
Attorney/Agent for Applicant(s)

MILLEN, WHITE, ZELANO
& BRANIGAN, P.C.
Arlington Courthouse Plaza 1, Suite 1400
2200 Clarendon Boulevard
Arlington, Virginia 22201
Telephone: (703) 243-6333
Facsimile: (703) 243-6410

Attorney Docket No.: DORRIE-0007

Date: January 26, 2007

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